Table 2
Association of atrophic knee OA with any progression of JSN and cartilage loss, compared to non-atrophic OA knees using both (radiographic and MRI) definitions of atrophic and non-atrophic OA.

OA phenotype (Radiographic definition)	Absence of progression of JSN	Any progression of JSN	Adjusted odds ratio	
			OR (95%CI)	p-value
Non-atrophic OA	224/373 (60%)	149/373 (40%)	1.0 (ref)	
Atrophic OA	54/77 (70%)	23/77 (3096)	0.6 (0.4, 1.0)	0.06
OA phenotype (Radiographic definition)	**Absence of progression of cartilage loss**	**Any progression of cartilage loss**	**Adjusted odds ratio**	
			OR (95%CI)	**p-value**
Non-atrophic OA	171/373 (46%)	202/373 (54%)	1.0 (ref)	–
Atrophic OA	45/77 (58%)	32/77 (42%)	0.6 (0.3, 1.0)	0.04
OA Phenotype (MRI Definition)	**Absence of Progression of JSN**	**Any Progression of JSN**	**Adjusted Odds Ratio**	
Non-atrophic OA			**OR (95%CI)**	**p-value**
	248/400 (62%)	152/450 (38%)	1.0 (ref)	–
Atrophic OA	30/50 (60%)	20/50 (40%)	1.2 (0.7, 2.3)	0.53
OA Phenotype (MRI Definition)	**Absence of Progression of Cartilage Loss**	**Any Progression of Cartilage Loss**	**Adjusted Odds Ratio**	
			OR (95%CI)	**p-value**
Non-atrophic OA	187/400 (47%)	213/400(53%)	1.0 (ref)	–
Atrophic OA	29/50 (58%)	21/50 (4296)	0.7 (0.4,1.3)	0.24

of up to one OARSI grade in at least one compartment), and fast progression (an increase of more than one OARSI grade in at least one compartment). Regarding progression of cartilage loss on MRI from baseline to FU, three groups were defined: no progression (same WORMS grade in all ten subregions), slow (an increase up to one WORMS grade, including within-grade increase, in at least one of the ten subregions), and fast progression (an increase of more than one WORMS grade in at least one of the ten subregions). Co-variance analysis was performed to test if there were differences between atrophic vs. non-atrophic knee OA phenotypes, using both (radiographs and MRI) definitions, regarding no progression, slow, and fast progression of JSN and cartilage loss. Logistic regression analysis with generalized estimated equations was performed to assess the association of atrophic knee OA with any progression of JSN and cartilage loss, compared to non-atrophic OA knees (reference group). The results were adjusted for age, gender, body mass index, tibiofemoral malalignment, progression of meniscal damage and extrusion.

Results: A total of 450 knees from 398 participants were included. Using the radiographic definition, there were 77 (17.1%) atrophic OA and 373 (82.9%) non-atrophic OA knees at baseline. Using the MRI definition, there were 50 (11.1%) atrophic OA and 400 (88.9%) non-atrophic OA knees. There were no significant differences between both groups (atrophic vs. non-atrophic) regarding fast progression of JSN or cartilage damage (Table 1). Logistic regression analysis using both definitions showed that the atrophic phenotype of knee OA was not at increased risk for progression of disease compared to the non-atrophic phenotype (Table 2). Using the radiographic definition, a modest protective effect against progression of MRI cartilage loss was demonstrated for atrophic OA knees when compared to the non-atrophic group (OR = 0.6 (95%CI 0.3, 1.0); p=0.04).

Conclusions: Based on these results, the atrophic phenotype of knee OA does not predispose OA joints to more rapid progression compared to non-atrophic OA. This finding might be of potential relevance for eligibility of participants with atrophic knee OA in aNGF programs who are commonly excluded due to potential increased risk for rapid progressive OA.

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CROSS-SECTINAL AND LONGITUDINAL ASSOCIATIONS BETWEEN SERUM LEVELS OF HIGH SENSITIVITY C-REACTIVE PROTEIN, RESISTIN AND KNEE BONE MARROW LESIONS IN PATIENTS WITH KNEE OSTEOARTHRITIS

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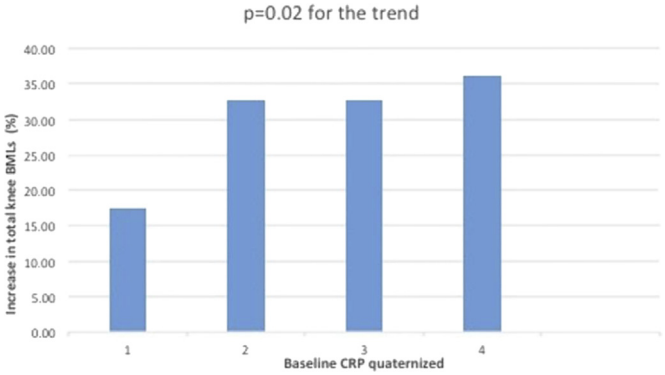
Purpose: Low-grade inflammation may play a role in osteoarthritis (OA). Although some studies reported that inflammatory markers such as high sensitivity C-reactive protein (hs-CRP) were increased in OA, the findings for associations between hs-CRP and OA are inconsistent. The link between serum levels of hs-CRP and bone marrow lesions (BMLs) in OA patientshas not been explored., Similarly, the findings for the associations between resistin and OA are controversial and little is known if resistin is associated with BMLs. The aims of this study were, therefore, to describe the association between serum levels of hs-CRP, resistin and BMLs cross sectionally and longitudinally in patients with knee OA.

Methods: A total of 188 patients (mean 63 years, range 50-79, female 53%) with symptomatic knee OA were selected from a randomised placebo controlled clinical trial studying the effect of vitamin D supplementation on OA. Serum levels of hs-CRP and resistin were tested at baseline and 24 months later using enzyme-linked immunosorbent assay (ELISA). T2 weighted fat-supressed fast spin echo magnetic resonance imaging (MRI) was performed at baseline and 24 months to assess compartmental and total knee BMLs scores and their changes using modified Whole-Organ MRI Score system (WORMS). Linear or logistic regression analyses were used to determine the association of baseline hs-CRP and resistin with total knee BMLs as well as changes or increases in BMLs before and after adjustment for age, sex, BMI, treatment (vitamin D / placebo) and CRP / resistin as appropriate.

Results: At baseline, quartiles of serum level of hs-CRP were associated with total knee bone marrow lesions in multivariable analyses (OR: 1.45 per quartile, 95% CI: 1.01, 2.09). Serum levels of resistin were associated with total knee BMLs (β:0.04 per ng/ml, 95% CI: 0.01, 0.08). Longitudinally, quartiles of serum levels of hs-CRP predicted increases in total knee BMLs (OR: 1.51 per quartile, 95% CI: 1.08, 2.12; Figure 1), and changes in serum levels of hs-CRP were associated with changes in total knee BMLs (β: 0.09, 95% CI: 0.04, 0.34). Baseline resistin levels were not significantly associated with change in total BMLs. Change in serum levels of resistin were only associated with changes in lateral tibiofemoral BMLs (β: 0.16, 95%CI: 0.01, 0.05) and not total knee BMLs (β: 1.01, 95%CI: 0.97, 1.04).

Conclusions: This is the first study to report that serum levels of hs-CRP are associated with total knee BMLs and predict worsening knee BMLs over 2 years in patients with knee OA, suggesting inflammatory involvement in the pathogenesis of BMLs. Serum resistin levels are associated with BMLs in knee OA, but the causal relationship is unknown.



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IDENTIFICATION OF AN INFLAMMATORY PHENOTYPE WITH HIGHER LIKELIHOOD OF PROGRESSION IN OA: ANALYSIS OF WOMAC PAIN SUB-QUESTIONS, C3M AND U-CTX-II FROM TWO PHASE 3 RANDOMIZED CLINICAL TRIALS WITH TREATMENT OF SYMPTOMATIC KNEE OSTEOARTHRITIS

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Purpose: There are three main tissues remodeled as part of osteoarthritis (OA); cartilage, bone and the synovial membrane, which may represent separate phenotypes that needs to be treated differently. Recent data has shown that type II collagen degradation (CTX-II) is a biomarker of cartilage and subchondral turnover. C3M is a biomarker of synovial inflammation and turnover. It is estimated that about 10-30% of OA patients have synovitis. The aim of the study was identify different subtypes of OA related to progression.
Methods: Fasting serum (n=767) and urine (n=620) samples were collected at baseline from patients with painful knee OA participating in the placebo arms of two phase III RCTs (NCT00486434 and NCT00704847). Serum C3M (MMP-derived type III collagen neo-epitope [Nordic Bioscience, Denmark]) and creatinine-corrected urinary CTX-II (type II collagen C-terminal telopeptide [IDS PLC, United Kingdom]) were measured. The relationship between the biomarkers and the 5 WOMAC pain subscale questions of the baseline-reported WOMAC pain level, using the sum of target and non-target knee, were analyzed: A; during walking on a flat surface, B; using stairs (up or down), C; at night while in bed, D; sitting or lying and E; while standing. Joint space width was analyzed at baseline and after 24 month. The data were analyzed by Spearman's correlations on log-transformed data and by backward multiple regression analysis, where WOMAC or radiographic scores were set as the dependent variable and biomarkers, age, gender and BMI as covariates.
Results: Levels of CTX-II significantly correlated with WOMAC with all 5 sub-questions ($p<0.01$), while level of C3M was correlated with question B and E ($p<0.05$). When adjusting for age, BMI, and gender, CTX-II remained significantly associated with all sub-questions: A) $r=0.20$, $p<0.0001$; B) $r=0.16$, $p=0.0005$; C) $r=0.11$, $p=0.017$; D) $r=0.13$, $p=0.0046$; and E) $r=0.17$, $p=0.0002$. C3M became non-significant; B) $r=0.08$, $p=0.063$ and E) $r=0.08$, $p=0.069$. CTX-II was significantly correlated to the mean JSW of the two knees ($r=-0.17$, $p<0.0001$), whereas C3M was significantly correlated to joint space narrowing of the target knee ($r=0.11$, $p=0.013$).
Conclusions: Diagnostically, urinary CTX-II was associated with all types of pain. Most prominent with WOMAC sub-question A, walking on a flat surface, which may indicate that CTX-II is related to pain coming from continuous skeletal load - supported by the strong correlation with JSW and previous data suggestion origins of subchondral bone turnover and articular cartilage. C3M, which are released in synovitis, was weakly correlated with B and E, using stairs and standing still, respectively. C3M was correlated to progression indicating that patients with elevated C3M and consequently synovial inflammation had a higher likelihood of being a progressor. These biomarkers may assist in identification of the inflammation driven OA phenotype, which needs to be treated different than non-inflammatory OA.

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IMPROVED PHENOTYPE DEFINITIONS OF OA IN GENETIC ASSOCIATION STUDIES HIGHLIGHT A STRUCTURAL ROLE FOR A COMMON VARIANT IN LRCH1

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Purpose: Osteoarthritis (OA) has a strong genetic component but the success of previous genetic association studies has been restricted due to insufficient sample sizes and phenotype heterogeneity. Differences in ascertainment criteria along with the highly heterogeneous clinical manifestations of OA have been proposed as likely factors behind the paucity of replication for genetic determinants of OA. The aim of our study is to identify hip OA susceptibility variants by examining a set of more homogeneous, radiographically-derived OA endophenotypes relating to specific anatomic pattern of joint involvement.
Methods: Hip OA subjects comprised in total 2,118 unrelated individuals of European ancestry from the arcOGEN genome-wide association study (GWAS). Inclusion criteria were radiographic evidence of hip OA (Kellgren Lawrence (KL) $\geq$ 2) and secondly, a set of minimum radiographic requirements defined as an antero-posterior (AP) view of the degenerate hip joint. Hip OA pattern was classified using standard photographic atlases as superior, axial, medial and concentric joint space narrowing. 1,817 cases had GWAS data on Illumina 610k and 301 cases had GWAS data on the HumanOmniExpress platform. We used 6,500 population-based, publically-available controls from the UK. Following 1000 Genomes-based imputation and stringent quality control we carried out association analyses at ~7million variants using the score test under an additive model and meta-analyses with the fixed-effects model. We carried out 2 types of association analyses: GWAS meta-analysis within OA cases by comparing i) hip OA cases characterised by axial/medial femoral head migration vs. all other hip OA cases and conversely hip OA cases characterised by superior femoral head migration vs. all other hip OA cases; and ii) GWAS of 1,817 hip OA cases stratified by anatomic pattern of joint involvement against publically-available controls.
Results: In the GWAS meta-analysis carried out across OA cases with axial/medial femoral head migration vs. all other hip OA cases the most significant association was observed for rs754106 in intron 1 of the LRCH1 gene (for allele T OR[CIs]=1.46[1.26-1.68]; p=2.9x10-7). Adjustment for gender did not attenuate the signal (p=5.7x10-6). Evidence for association was strong and consistent across both GWAS sets despite the small sample size of the second study (p=1.1x10-5, N=425/1392; p=0.004, N=76/225). Conversely in the GWAS meta-analysis carried out across OA cases with superior femoral head migration vs. the rest (N=1469/647) rs754106 is also the most significant locus (p=1.1x10-7) but the T allele is protective (OR=0.7). In the association analysis of hip OA patients with axial/medial femoral head migration vs population-based controls we still find strong evidence for association at rs754106 (p=0.00015, OR 1.31[1.13-1.5]) but when we analyse all hip OA cases together vs. the same control set the signal is fully attenuated (p= 0.89).
Rs754106 is in intron 1 of Leucine-Rich Repeats And Calponin Homology (CH) Domain Containing 1 (LRCH1/CHDC1) gene. Genetic associations with knee OA at variants spanning intron 1 of LRCH1 were previously reported but the most significant association was observed at rs912428 (for allele T OR[CIs] =1.44[1.18-1.79]; p<5x10-4, N=1978/1798) which is located 15kb away from rs754106 (D'=1, r2=0.242). Similar trends in allele frequencies were observed for samples with hand and hip OA but were not significant. Subsequent publications examining the role of this variant in knee or hip OA yielded conflicting results while a synthesis of genetic association studies to date reported an OR of 1.17 with nominal significance and moderate heterogeneity. Our findings indicate that the paucity of replication at this locus stems from the differences between prevalence of pattern of joint involvement in the different cohorts.
Conclusions: By partitioning the hip OA phenotype according to specific anatomic pattern of joint involvement we detect a common variant in LRCH1 and highlight the structural role of this gene in OA. We conclude that in a highly heterogeneous disease like OA precise phenotype definition is crucial for empowering the detection and replication of OA susceptibility loci and can provide important insights into the specific processes of OA.

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JOINT RELATED NEUROPATHIC PAIN IS ASSOCIATED WITH LOSS OF JOINT SPECIFIC FUNCTION AND QUALITY OF LIFE WITHIN HIP AND KNEE OSTEOARTHRITIS PATIENTS

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Purpose: In the past decade it became clear that Osteoarthritis (OA)-pain is not solely nociceptive-driven. Changes within the peripheral and central nervous system are probably accountable for accessory pain amplification and sensitization. It is believed that central sensitisation (CS) in combination with peripheral nerve disruption may manifest in OA-pain with neuropathic features. Based on previous studies it's known that about 20-37% of the hip/knee OA patients possess a possible or likely neuropathic pain (NP) phenotype (painDETECT-score >12). As known,